486

CLASSIFICATION SYSTEM OF CHRONIC GVHD IMPACTS RISK FACTORS

Jacobs, R.W., Chen, H., Savani, B.N., Kassim, A., Clifton, C., Vaughan, L.A., Lucid, C.E., Jagasia, M. Vanderbilt University Medical Center, Nashville, TN

Risk factors associated with chronic graft-versus-host-disease (cGVHD) after allogeneic hematopoietic cell transplantation have been studied using the limited/extensive (L/E) classification. In 2005, the NIH criteria were proposed and have been validated as a prognostic tool in retrospective studies. It is unclear if the previously identified risk factors of cGVHD apply to cGVHD as defined by NIH criteria. At our center, patients undergoing allo-HCT with a survival of > 100 days are transitioned to the Long Term Transplant Clinic. Grading and staging of GVHD using NIH criteria (including severity) and L/E classification has been done prospectively since 2006. We analyzed risk factors associated with GVHD after day 100 and compared the factors using both classifications. Patients characteristics are summarized in Table 1(n = 205, cord transplant excluded). All 11 risk factors were analyzed using univariate analysis.

Table 1. Patient characteristics

Risk Factor	Variable	N (205)	%
1	Age, median, (range) years	47 (18-70)	
2	Regiment Intensity:		
	Ablative/other	110/94	54/46
	TBI*: yes/no	75/129	37/63
3	Gender:		
	Female donor-> male recipient/other	54/140	28/72
4	Donor Type:		
	Related/Unrelated	120/84€	59/41€
5	Stem Cell Source:		
	Peripheral Blood/Bone Marrow	166/39	81/19
6	Disease Risk Status (CIBMTR)		
	Low	105	51
	Intermediate	61	30
	High	26	13
7	CMV #:		
	R/D¥ +/+ vs. other	68/130	34/66
8	Acute GVHD-maximum grade:		
	0-1 vs. 2-4	53/143	27/73
9	Day 100 - on steroids:		
	Yes/No	87/110	44/56
10	Platelet count (x 10∧9/L):		
	< 100 vs. ≥ 100	80/116	41/59
11	Day 100 total bilirubin (mg/dL):		
	Median (range)	.8 (.2-2.6)	
	Limited/extensive GVHD Classification		
	None	44	21
	Limited	33	16
	Extensive	128	62
	NIH Criteria - GVHD Classification		
	None	44	21
	Acute subtypes	33	16
	Classic/Overlap cGVHD	128	62
	Severity∂		
	Mild	6	5
	Moderate	55	43
	Severe	65	51

*Total body irradiation, # CMV-cytomegalovirus, ¥ R/D-recipient/donor, ∂ applicable for classic/overlap cGVHD only, € 37/84 unrelated donors received in-vivo T-cell depletion.

GVHD beyond day 100 was seen in 151 of 205 patients (76%). Bone marrow (BM) (versus PBSC) as graft source (61% vs. 82%, P < 0.001), and use of in vivo T-cell depletion (versus no T-cell depletion) (54% vs. 84%, P < 0.0001) was associated with decreased L/E cGVHD. Using the NIH classification, BM (38% vs. 70%, P = 0.003) and in vivo T cell depletion (32% vs. 73%, P < 0.001) had a lower incidence of classic/overlap cGVHD compared to no GVHD. Grade 2-4 acute GVHD (aGVHD) and use of steroids for aGVHD at day 100 was associated with a higher incidence of acute subtypes/no GVHD beyond day 100 compared to classic/overlap cGVHD (69% vs. 31%, P = 0.018; 67% vs. 33%, P = 0.052). Adjusted for donor type, aGVHD, and day 100 steroid use, only BM as stem cell source was an independent predictor of decreased L/E cGVHD (OR 0.37, P = 0.017). BM as stem cell source, remained an independent factor for decreased classic/overlap cGVHD (OR 0.3, P = 0.009). The 2 yr overall survival (OS) for the entire cohort was 86% (95% CI, 81.6- 92). Patients with classic/overlap cGVHD had a superior OS compared to acute subtypes/none (P = 0.005). Only stem cell source (BM) remained an independent predictor of OS (HR 2.38, 95% CI 1.05-5.41, P = 0.039).

This study shows that graft source remains an important risk factor of cGVHD irrespective of the classification system, but the incidence of cGVHD using the NIH criteria is significantly lower. Other known risk factors of L/E cGVHD were not predictive of cGVHD as defined by the NIH criteria.

487

MAST CELLS SUPPRESS GVHD IN A MECHANISM INDEPENDENT OF $CD4^+CD25^+$ REGULATORY T CELLS

Leveson-Gower, D.B.[1], Sega, E.I.[1], Kalesnikoff, J.[2], Florek, M.[1], Galli, S.J.[2], Negrin, R.S.[1] [1] Stanford University, Stanford, CA; [2] Stanford University, Stanford, CA

Mast cells, which are important mediators of both innate and adaptive immune responses, have been shown to have anti-inflammatory roles in some experimental models. Previous studies have hypothesized that $CD4^+CD25^+$ regulatory T cells (Tregs) may "recruit" mast cells as part of a mechanism of inducing tolerance to allografts, and also that mast cells may be able to induce $CD4^+$ T cells into $CD4^+CD25^+Foxp3^+$ cells. In this study, we explored whether the suppression of graft-versus-host disease (GVHD) by Tregs involves mast cells in a major MHC-mismatch model of GVHD. C57BL/6 ($H\text{-}2^b$) recipient mice were treated with myeloablative irradiation and $5x10^6$ T-cell depleted bone marrow cells (TCD-BM) from FVB/N donors ($H\text{-}2^q$), followed by transfer of $2x10^6$ FVB/N CD4 and CD8 conventional T cells (Tcon) to induce GVHD. To suppress GVHD, groups were given Treg at a Treg:Tcon ratio of 1:3. Equivalent suppression of GVHD was observed with Treg in both wild-type C57BL/6 or C57BL/6-$Kit^{W\text{-}sh/W\text{-}sh}$ recipient mice (which virtually lack mast cells), indicating that Treg suppression of GVHD in this model did not involve mast cells. Furthermore, the percentage of Foxp3 positive Treg cells was similar before and after transplantation in $Kit^{W\text{-}sh/W\text{-}sh}$ and WT recipients, and $CD4^+CD25^{hi}$ Treg from $Kit^{W\text{-}sh/W\text{-}sh}$ mice were equally capable of suppressing T cell proliferation in a mixed leukocyte reaction. However, survival of recipients receiving TCD-BM and Tcon only was significantly reduced in animals lacking mast cells, where 100% of $Kit^{W\text{-}sh/W\text{-}sh}$ recipients died by day 15 of transplantation, yet over 50% of WT recipients were alive at day 60 ($p < 0.0001$). While IL-10 was present at low-levels in the serum of wild-type recipients of Tcon (mean50 pg/mL), IL-10 was undetectable in the serum of $Kit^{W\text{-}sh/W\text{-}sh}$ recipients. Furthermore, preliminary experiments have indicated that $Kit^{W\text{-}sh/W\text{-}sh}$ that have had their gut and other sites engrafted by transfer of $5x10^6$ bone marrow-derived cultured mast cells (BMCMCs) i.p., have improved survival over untreated $Kit^{W\text{-}sh/W\text{-}sh}$, but not if BMCMCs were derived from $IL\text{-}10^{-/-}$ mice. Finally we observe that $Kit^{W\text{-}sh/W\text{-}sh}$ have greatly increased amounts of Tcon proliferation in lymph node, liver, and gastrointestinal tract tissue sites, as indicated by bioluminescence imaging (BLI) ($p < 0.001$). Thus, we propose that the presence of mast cells significantly reduces GVHD, independent of Treg, by releasing IL-10 and decreasing Tcon proliferation.

488

CYCLOSPORINE AND METHOTREXATE (CSA/MTX) COMPARED WITH CYCLOSPORINE AND MYCOPHENOLATE MOFETIL (CSA/MMF) AS GVHD PREVENTION REGIMENS IN ALLOGENEIC STEM-CELL TRANSPLANTATION FROM UNRELATED DONORS; RELATIVE OUTCOMES ARE DEPENDANT ON DISEASE STATUS AT TRANSPLANTATION

Shimoni, A., Shem-Tov, N., Rand, A., Roth, S., Volchek, Y., Yerushalmi, R., Nagler, A. Chaim Sheba Medical Center, Tel-Hashomer, Israel

Allogeneic stem cell transplantation (SCT) from matched unrelated donors (MUD) is a potentially curative approach in patients (pts) with hematologic malignancies and no sibling donor. Several GVHD prevention regimens have been used but there is no data